

Neuromodulation of Bilateral Hippocampal Foci, an Alternative for Mesial Temporal Lobe Seizures in Patients with Non-Lesional MRI: Long-Term Follow-up

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Abstract

Background: Patients with bilateral independent hippocampal refractory seizures, who show no evidence of lesion in the MRI, constitute a challenge for their treatment. The risk of severe retrograde amnesia and/or residual seizures is high when bilateral temporal lobectomy is performed. Several groups have reported electrical neuromodulation of the hippocampus as a reversible surgical alternative for mesial temporal lobe epilepsy seizures that are refractory to medical treatment.

Methods: In the Epilepsy Clinic of the General Hospital we have had three patients with bilateral independent foci and non-lesional MRI. The present publication shows their long-term seizure status and their neuropsychological outcome. Stimulation parameters were 3.0 V amplitude, high frequency (130 Hz), 450 µs pulse width, one minute ON and 4 min OFF cyclic stimulation. Follow-up extended over 9 years.

Results: Patients showed dramatic seizure reduction. In two patients in whom stimulation was stopped (due to battery depletion or skin erosion), seizure reduction persisted for months after stimulation stopped, but eventually seizures reappeared slowly. One patient has had uninterrupted stimulation and has been seizure free for nine years. The neuropsychological tests showed no functional decrease at the selected modulation parameters.

Conclusion: Bilateral hippocampal stimulation is effective in seizure control in patients in whom ablative surgery is not recommended.

Introduction

The death of Henry Molaison (HM) in December 2008, kindled the discussion based on the postmortem analysis of one of the most emblematic cases in epilepsy surgery [1]. This patient had bilateral mesial temporal lobe seizures that were refractory to several antiepileptic medications. In an attempt to control his seizures, at age 27, a bilateral temporal lobectomy with amygdalo-hippocampectomy was performed. Since this moment on, his life changed [2]. Even though his seizures were mostly controlled by the procedure, the surgery rendered severe anterograde amnesia.

Numerous neuropsychological, imaging and anatomic studies were performed [3]. The conclusion of these studies indicates that bilateral temporal lobectomy is a high-risk surgery due to its neurological consequence. Even though patients with refractory mesial temporal lobe seizures are candidates for temporal lobectomy [4,5] patients are rejected for ablative surgery if they have bilateral independent hippocampal epileptic foci [6]. The prognosis is worsened if there is no evidence of hippocampal sclerosis in the MRI [7]. Refractory bilateral seizures are a challenge for every epileptologist, neurologist and neurosurgeon.

In 2000 our group proposed electrical stimulation as a feasible alternative [8] for mesial temporal lobe epilepsy and other authors have confirmed the positive results of this method [9-13]. Since our initial publications no neuropsychological deficit has been observed at low amplitude stimulation parameters, other investigators have confirmed this finding [14-16]. Herein we present a long-term follow-up in seizure control and neuropsychological outcome of three patients who had no evidence of hippocampal sclerosis in the MRI and showed bilateral independent epileptic foci evidenced by intracranial recordings.

Methods

The hippocampal focus stimulation protocol was approved by the Research and Ethics Committees of the General Hospital of Mexico. Nine patients were included initially. In the present paper we present the long-term outcome of three patients from this group, those who had bilateral independent hippocampal foci demonstrated by depth electrode recordings. The three patients had bilateral hippocampal stimulation directed to the epileptic foci. Two males and one female are described, ages 44, 21 and 24 years old, respectively. Complex

partial seizures with secondary generalization started at 3, 12 and 11 years, respectively.

Surface EEG showed bilateral temporal spikes and MRIs did not demonstrate hippocampal lesion. Neuropsychological battery was performed including the Neuropsi Attention and Memory Battery [17-18]. This is a comprehensive battery developed for evaluating attention, memory, and executive functions. The tests have been standardized and validated in Spanish-speaking subjects from 6 to 85 years of age.

The results were corrected according to age and education. Subtests are organized into summary index counts that yield a Total Attention and Memory Index score, as well as separate ones for Attention and Memory Processes. One patient had mild verbal memory impairment and two had normal tests. Batteries were applied in the baseline phase, 6 and 12 months with neuromodulation and once a year afterwards.

In an attempt to determine the precise location and the laterality of the epileptic foci, patients were included in phase II invasive study protocol. Octopolar AD-Tech [Racine WN] depth electrodes were implanted through occipital burr holes (Figure 1A).

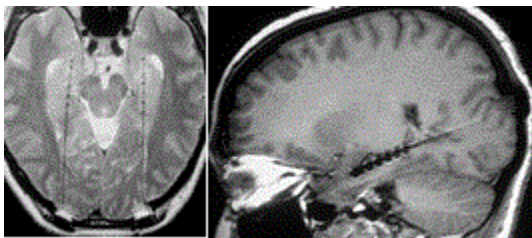


Figure 1(A): Depth electrodes were implanted through occipital burr holes.

To direct the trajectory of the electrodes, we used the Praezis 3.0 Plus program using pre operative MRI. During implantation we performed fluoroscopic control and images of final site were taken. Once implanted, patients underwent MRI to verify correct implantation and afterwards, antiepileptic medication was tapered and continuous video EEG monitoring was performed until several spontaneous seizures arising independently from right and left anterior hippocampus were recorded, confirming bilateral foci (Figure 1B and 1C).

Patients were informed of their results and invited to participate in the neuromodulation protocol. Diagnostic electrodes were removed and substituted by 3387 DBS by Medtronic Inc. Minneapolis, MN. Again, we used Praezis 3.0 Plus, planning the trajectory of therapeutic electrodes based on preoperative MRI and diagnostic electrode position with post implantation MRI. They were directed so that 3 contacts of the DBS electrode were within the area where the epileptic foci were localized.

Fluoroscopic control was undertaken during implantation, the trajectory and location of the DBS electrodes to the fluoroscopic scans of the diagnostic electrodes were compared. MRI scans were obtained again to confirm target and afterwards the pulse generator (IPG_Itrel 3 by Medtronic) was connected. Stimulation parameters were set as follows: 3.0 V, 130 Hz, 450 μ s, cycling 1 min ON and 4 min OFF. All patients were OFF stimulation during the first month to discard implantation effect and were enrolled in a double blind study during

the first three months. This report includes the open label phase of all patients.

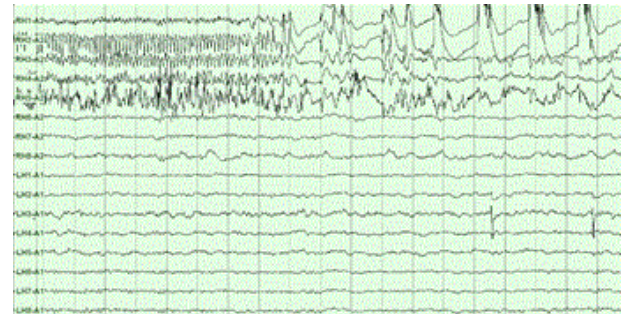


Figure 1(B): Patient's 1 right hippocampal seizure onset.

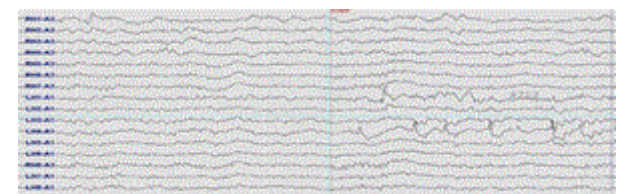


Figure 1(C): Patient's 1 left hippocampal seizure onset.

Results

Stimulating contacts position

Figure 2 shows stimulated contact position in each patient. Note that the electrodes were directed to the epileptic foci, not a specific structure. Patient 1 had right contact in dentate gyrus and left one in CA1. Patient 2 had both right and left contacts in dentate gyrus and patient 3 had right contact located in parahippocampus and left one in subiculum. The long-term follow-up was 120 to 167 months.

Seizure decrease

Figure 3 shows the seizure count graphs for each patient. Patient 1 was the first bilateral case selected for chronic stimulation. As such we did not know if bilateral stimulation would cause neuropsychological problems. This is why initially he was stimulated on the right hippocampal focus during 6 months. He had 50% seizure decrease. On month 7, bilateral stimulation started and seizures continued decreasing until he became seizure free during 9 months. At the end of month 29, he had 3 complex partial in a single day due to battery depletion. Pulse generators were changed. He remained with one seizure every 3 months from month 15 till month 71. On month 72 he had one complex partial seizure with secondary generalization due to battery depletion and was not able to afford pulse generators again. Seizures have increased progressively, but never reached basal numbers.

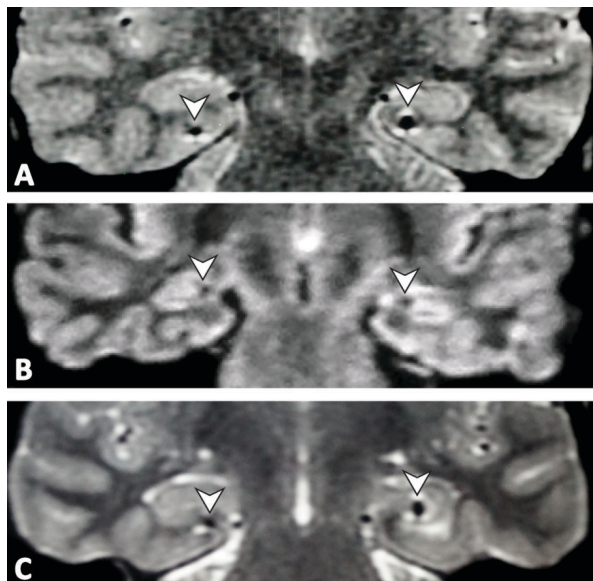


Figure 2: MR1 T2 weighted showing bilateral stimulated contacts position in each patient.

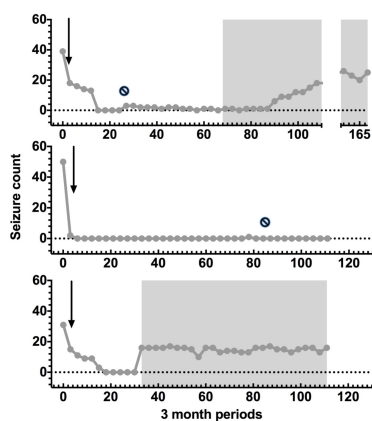


Figure 3: Graphs of the seizure counts every 3 months. Arrows show the month when stimulation is turned ON. All patients had a decrease in their seizure counts during stimulation periods and never returned to basal counts after stimulation showed its positive effect, regardless if the batteries continued working. Crossed circles show when batteries were replaced. Shadow indicates time when patient was not stimulated.

Patient 2 had a dramatic seizure decrease during the first three months of stimulation and remained seizure free till month 81 when

three complex partial seizures appeared due to battery depletion. Pulse generators were changed immediately and patient has remained seizure free.

Patient 3 had a progressive seizure decrease during 18 months and afterwards she was seizure free. On month 31 she had to be explanted due to skin erosion. Since then seizures increased but never returned to baseline numbers remaining 50% reduction.

Neuropsychological testing

Table 1 shows the three patients' results comparing baseline grades with 1 year of neuromodulation. Note that none of the patients had a decrease in their performance, they either stayed the same or improved compared to baseline.

Figure 4 neuropsychological results of patient 1 at two different measurements: baseline and 2 years of stimulation. Note that the patient showed improvement in almost all skills during stimulation compared to baseline. Neuropsychological testing grades of patient 2 were good before and during stimulation, but he improved specifically in verbal memory and this is important since he has had a very successful development, graduating as Master in Foreign Languages at the University, speaks fluently German, English and French. Patient 3 maintained her neuropsychological performance in same levels.

Discussion

Several groups have performed hippocampus stimulation and have found a beneficial result in seizure reduction. Compared to other stimulation targets it has a better outcome. Vagal stimulation reduces seizures in best cases 45% [19]. Responsive stimulation shows a progressive seizure reduction that takes several years to show 45% seizure reduction [20]. In our previously published studies, Patients with no MRI evidence of mesial temporal sclerosis had a >95% seizure reduction. This decrease in seizures takes 1 to 2 months. The difference between the responsive stimulation and our open loop cyclic mode can be explained due to difficulty in having a reliable seizure prediction system. Currently there are a number of groups working on seizure detection and their results could improve the results of the responsive stimulation mode [21-24].

All patients reported herein, had seizure reduction. It has been suggested that the intra hippocampal electrode insertion per se, results in seizure remission [25,26]. This study shows that seizure control happened in different times: two (patient 2), fifteen (patient 1) and eighteen months (patient 3). The reason for the differential response to DBS is unknown, but delay in seizure reduction indicates that antiepileptic effect was not secondary to micro lesion produced by implantation of recording and DBS electrodes. The fact that seizure control depended on DBS and was not the result of spontaneous remission is clearly illustrated in Figure 3, where one can see that battery depletion or explantation was associated with recurrence of seizures.

However, seizure recurrence did not occur abruptly but progressively increased over a period of months (Case 2) to over a year and a half (Case 1), which indicates that the antiepileptic effect extends beyond DBS, as has been described in cerebellar [27] and thalamic [28] stimulation. This stresses the importance that studies using double blind phases place the maneuver at the beginning of chronic stimulation and avoid cross over.

Patient	Education level	Basal performance	Attention memory &	Verbal memory	Digit counting	Logic memory	Visual reproduction	Wind mill	Bezars
1	Elementary	Poor	No changes	Improved	improved	No changes	Improved	Improved	Improved
2	University	Good medium percentiles	Improved	Improved	improved	Improved	No changes	No changes	No changes
3	Technical career	Good lower percentiles	No changes	No changes	No changes	No changes	No changes	No changes	No changes

Table 1: The three patients' results comparing baseline grades with 1 year of neuromodulation.

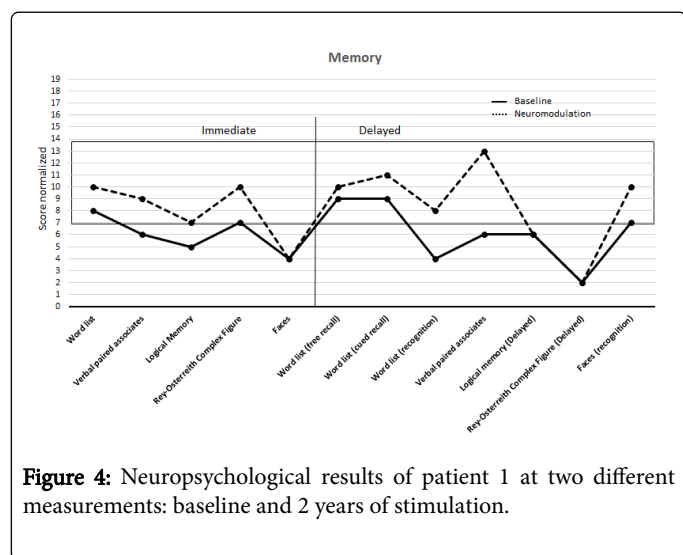


Figure 4: Neuropsychological results of patient 1 at two different measurements: baseline and 2 years of stimulation.

Bilateral Anterior Temporal Lobectomies (ATL) produces severe memory deficit. In contrast, bilateral Hippocampal Electrical Stimulation (HES) did not induce neuropsychological deterioration in our cases. Moreover, in our case 3, posterior HES in the right side was accompanied by normalization of a mild deficit for non-verbal memory one year after the onset of stimulation, as reported by Boex [29]. In this case improvement in memory occurred when monthly seizures had decreased by 80% and in Patient 1 memory improvement was detected when patient was seizure free. Case 2 had normal memory performance and remained so. Therefore, bilateral simultaneous HES for seizure control does not seem to interfere with memory function and might enhance memory, as reported by Boex [29]. Neuropsychological improvement has been reported with centromedian thalamic stimulation in cases with Lennox-Gastaut and clearly relates to seizure control and normalization of the EEG background [30-32].

There has been discussion regarding the precise stimulation target. Our group has suggested that it should be directed to the epileptic focus and others to the subiculum [33]. In this report patient 1 had both stimulating contacts positioned in the area corresponding to the epileptic foci [32]. Patient 2 had both contacts very near the epileptic focus in the dentate gyrus. Patient 3, who took the longest time to achieve seizure freedom (18 months), had one of the contacts in the subiculum and the other in the para hippocampus.

Two of the patients had skin erosions over the skullcap used to hold DBS electrodes (Case 1) and the connector between DBS and

extension cable (Case 3) in the retro auricular area. This type of complications has been described previously [34]. Unfortunately neuromodulation could not be prolonged due to economic reasons.

Conclusion

Stimulation of the hippocampus epileptic foci is effective in controlling mesial temporal lobe seizures; it does not interfere with memory process when applied bilaterally. For the moment being, we report 3 cases, but in the future it may become a less invasive alternative for refractory cases. The efficacy is still related to some factors that are not fully known, such as the most effective place of stimulation in the hippocampal formation and optimization of stimulation parameters. Future work in the improvement of hardware for this indication should include single recording-stimulation electrodes with an increase in number of contacts, spaced to cover the entire hippocampus so that the patient can undergo a single surgical implantation to localize the epileptic focus and afterwards stimulate it. This would reduce costs and risks. And to avoid the system rejection for epileptic patients, the length of DBS electrodes should be reduced.

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